Meta-Analyses of Human Cell-Based Cardiac Regeneration Therapies : Response to Gyöngyösi, Wojakowski, Navarese, Moyé, and the ACCRUE Investigators

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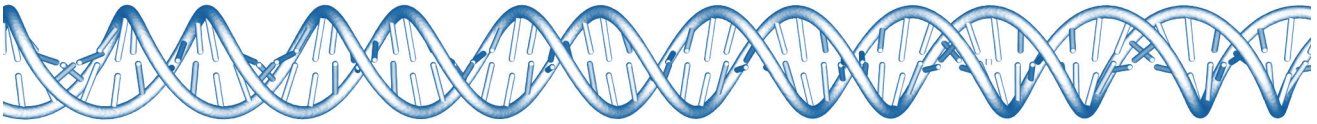

Meta-Analyses of Human Cell-Based Cardiac Regeneration Therapies

Controversies in Meta-Analyses Results on Cardiac Cell-Based Regenerative Studies

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Abstract: **In contrast to multiple publication-based meta-analyses involving clinical cardiac regeneration therapy in patients with recent myocardial infarction, a recently published meta-analysis based on individual patient data reported no effect of cell therapy on left ventricular function or clinical outcome. A comprehensive review of the data collection, statistics, and the overall principles of meta-analyses provides further clarification and explanation for this controversy. The advantages and pitfalls of different types of meta-analyses are reviewed here. Each meta-analysis approach has a place when pivotal clinical trials are lacking and sheds light on the magnitude of the treatment in a complex healthcare field. (*Circ Res*. 2016;118:1254-1263. DOI: 10.1161/CIRCRESAHA.115.307347.)**

Key Words: heart failure ■ myocardial infarction ■ meta-analysis ■ outcome measures ■ stem cells

The Meta-Analysis of Cell-Based Cardiac Studies (ACCRUE) consortium recently published the results of the first prospective individual patient data (IPD)–based meta-analysis that included 12 randomized clinical trials investigating 1-year outcomes in patients with recent ST-segment–elevation myocardial infarction (STEMI), who received intracoronary autologous stem and progenitor cells.[1] This IPD meta-analysis showed no effect of intracoronary autologous cell-based therapy on left ventricular function and clinical outcome in patients with recent STEMI. This contradicts some data from several small- or medium-sized single- and multicenter studies and multiple publication-based meta-analyses involving clinical cardiac regeneration in STEMI. Although de Jong et al[2] recently reported no difference between the cell therapy and control groups if the left ventricular parameters were measured by cardiac magnetic resonance imaging (cMRI), and the clinical end points (adverse events) were not significantly different in most of the meta-analyses, the major question is, why publication-based meta-analyses were in agreement, reporting beneficial effects of autologous reparative cell therapy in recent STEMI, but the IPD-based meta-analysis reported a negative outcome.[1] A thorough review of the data collection, statistics, and overall principles of meta-analyses may provide some answers and useful insights to interpret current findings.

Counterpoint, see p 1264
Response by Martin-Rendon, see p 1263

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*A list of all ACCRUE study participants is given in the Appendix.

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Nonstandard Abbreviations and Acronyms	
ACCRUE	Meta-Analysis of Cell-Based Cardiac Studies
cMRI	cardiac magnetic resonance imaging
EDV	end-diastolic volume
EF	ejection fraction
ESV	end-systolic volume
IPD	individual patient data
STEMI	ST-segment–elevation myocardial infarction

Summary of Aggregate and IPD Meta-Analyses of Studies Including Patients With Recent STEMI and Intracoronary Cell Therapy

A summary of the meta-analyses of randomized trials in patients with recent STEMI receiving intracoronary cell-based therapy is provided in Table 1, showing the results of the efficacy outcome parameters.[1–21] The meta-analyses of clinical studies involving patients with chronic ischemic heart disease who received percutaneous intracoronary or intramyocardial or direct (during coronary artery bypass surgery) intramyocardial cell-based therapy are listed in Online Table I and References I–V. The main results of the meta-analyses, including all cardiac studies with cell-based therapy irrespective of randomization, cell type, or delivery mode, are provided in Online Table II and References VI–IX.[19–21] The first analysis of the ACCRUE database reported the outcome of patients with recent STEMI randomized to intracoronary cell-based versus placebo therapy; therefore, this review concentrates on the discordance between the actual ACCRUE data and the data from the meta-analyses listed in Table 1.

Heterogeneous Outcomes Regarding Left Ventricular Function and Remodeling in Meta-Analyses

The cardiac efficacy end point of all meta-analyses was the change in ejection fraction (EF), and most of the meta-analyses also reported changes in end-diastolic volume (EDV) and end-systolic volume (ESV). There have been heterogeneous outcomes regarding left ventricular function and remodeling, expressed as changes in EF, EDV, and ESV in meta-analyses (Table 1). Aggregate data meta-analyses suggested that there was a benefit from cell-based therapy, based on significant increases in EF when compared with controls, whereas IPD analysis did not support this. There was a significant improvement in EF in 16 of the 17 meta-analyses of STEMI patients with cell therapy, and 10 of these analyses reported a significant decrease in ESV with a parallel significant decrease in EDV in 4 studies (Table 1). Decreases in ESV and EDV have particular importance in the assessment of left ventricular systolic function and remodeling. However, as the EF is derived from the EDV and ESV, parallel changes in both these measures might lead to an unchanged or similar calculated EF value, which should be considered in left ventricular function outcome studies.

One of the 3 meta-analyses assessing EF changes by cMRI showed no significant difference between cell treated and control patients (Table 1).[2] The ACCRUE did not include a subgroup analysis of EF measurement by cMRI, as significantly (P<0.001) more patients in the cell-treated group were evaluated using cMRI than the controls, because of 2:1 randomization of some included studies (eg, Myocardial Regeneration by Intracoronary Infusion of Selected Population of Stem Cells in Acute Myocardial Infarction [REGENT] Trial, Use of Adult Autologous Stem Cells in Treating People 2 to 3 Weeks After Having a Heart Attack [The LateTIME Study], Use of Adult Autologous Stem Cells in Treating People Who Have Had a Heart Attack [TIME], Swiss Multicenter Intracoronary Stem Cells Study in Acute Myocardial Infarction [SWISS-AMI]).[1,22–25] cMRI was used to quantify left ventricular function in 7 of 12 studies included in the ACCRUE analysis, and 6 of the 7 reported no difference between the cell-treatment and control groups on EF, EDV, and ESV (REGENT, LateTIME, TIME, SWISS-AMI, Cardiosphere-Derived Autologous Stem Cells to Reverse Ventricular Dysfunction [CADUCEUS], and Intracoronary Stem Cell Therapy in Patients With Acute Myocardial Infarction [SCAMI]).[22–27] Nevertheless, the methods for evaluation of left ventricular function and remodeling parameters were inconsistent between the studies included in the ACCRUE, as mentioned in the original article.[1]

In contrast to the IPD approach, clinical and statistical heterogeneity was greater (≤92.2%)[3] with aggregate data pooling in the standard meta-analytic approach, based on the calculation of mean difference in EF between the groups. According to the large variability between the studies included in the publication-based meta-analyses, a larger change in EDV (−4.6 mL) or ESV (−4.47 mL) was not significant, which was in contrast to the much smaller but significant change (EDV of −0.18 mL or ESV of −0.25 mL) reported in other publications.[4,7,10,14] Although intratrial variability may provide an explanation, the observed effect sizes raises the question of clinical relevance for the change in EDV and ESV in these reported ranges (−4.16 to +1.2 mL and −7.4 to −0.25 mL, respectively).

An evaluation of the relationship between the sample size of the meta-analyses and the time sequence of publications demonstrates a narrowing difference between cell-based treatment and control patients on changes in EF (Figure 1). The larger studies are more likely to be recent because of increasing numbers of individual studies being published. Larger meta-analyses included not only more patients but also more studies. There are profoundly different methodological and interpretative challenges between a meta-analysis consisting of 2000 patients from 2 studies and 1 with 2000 subjects from 50 studies. This perspective is helpful when considering the relationship between effect size and sample size. Larger meta-analyses tend to show smaller but significant changes in effect sizes. Although the larger meta-analyses may be associated with a smaller change in EF on average, increasing the number of studies (with growing variability between the separate nonsynchronized studies) in the larger meta-analyses may enhance the background noise, making it harder to discern the signal (effect) identified by smaller homogeneous studies.[28] Thus, both the number of studies and the sample size included in meta-analyses determine their importance.

Mortality and Adverse Events Paradox in Meta-Analyses

The clinical end point results of the meta-analyses are listed in Table 2. Apart from mortality, evaluation of clinical adverse

Table 1. List of Meta-Analyses of Studies Including Patients With Recent Acute Myocardial Infarction and Intracoronary Cell-Based Regenerative Therapy; Efficacy in Terms of Left Ventricular Function and Remodeling

Meta-Analyses on Cardiac Cell-Based Therapies	Year	Type of Meta-Analysis	No. of Studies	Sample Size	FUP, mo	EDV Changes, mL	ESV Changes, mL	EF Changes, %	If MRI, Changes in EF, %
Hristov et al[3]	2006	RCT-Pb	5	482	4–6	nr	nr	4.21*	nr
Lipinski et al[4]	2007	RCT-Pb	10	698	6	−4.6	−7.4*	3.0*	nr
Martin-Rendon et al[5]	2008	RCT-Pb	13	811	3–6	−2.47	−4.74*	2.99*	nr
Zhang et al[6]	2009	RCT-Pb	6	525	5	−0.15	n.a.	4.77*	nr
Zhang et al[7]	2009	RCT-Pb	7	660	6	−0.15	−0.25*	4.04*	Nr
Bai et al[8]	2010	RCT-Pb	10	814	6	nr	Nr	3.79*	Nr
Kuswardhani et al[9]	2011	RCT-Pb	10	906	4–60	−3.08*	−5.52*	2.07*	Nr
Takagi and Umemoto[10]	2011	RCT-Pb	15	877	nr	−0.18*	−0.35*	2.87*	Nr
Clifford et al[11]	2012	RCT-Pb	33	1765	<12	−3.52*	−4.47*	2.87*	1.78*
Zimmet et al[12]	2012	RCT-Pb	29	1830	3–6	−3.39*	−3.51*	2.7*	nr
Delewi et al[13]	2012	RCT-Pb	16	1641	3–6	nr	nr	2.55*	0.16*
Chen et al[14]	2013	RCT-Pb	5	510	nr	−2.29	−4.47	4.18*	nr
Jeong et al[15]	2013	RCT-Pb	17	1072	3–6	−3.46	−4.98*	2.51*	nr
de Jong et al[2]	2014	RCT-Pb	22	1513	6	−2.8	−4.05*	2.1*	0.13
Liu et al[16]	2014	RCT-Pb	8	262	6–24	0.69	−0.99	3.17*	nr
Gyöngyösi et al[1]	2015	RCT-IPD	12	1275	12	1.2	0.4	0.96	nr
Cong et al[17]	2015	RCT-Pb	17	1318	12	−1.69	−3.92*	2.74*	nr

Meta-analyses focusing on specific outcome, eg, imaging or long-term outcome or including patients with chronic ischemic heart diseases or cohort studies are excluded.[18–21] Comments to Table 1: Bai et al[8] divided the Meluzin study into 2 parts, the Bone Marrow Transfer to Enhance ST-Elevation Infarct Regeneration (BOOST) study included twice (with the 6- and 18-month results); Kuswardhani et al[9] same studies with different FUPs or subgroups included as separate studies; Zimmet et al[12] intracoronary cell therapy with/without granulocyte-colony stimulating factor pooled; Delewi et al[13] summary data of subgroups included. EF indicates ejection fraction; EDV, end-diastolic volume; ESV, end-systolic volume; FUP, follow-up; IPD, individual patient data based; MRI, magnetic resonance imaging; nr, not reported; Pb, publication based; and RCT, randomized controlled trial.

*$P<0.05$.

events in publication-based meta-analyses is difficult because the end points of the separate studies have heterogeneous definitions. Approximately one third of trials included hospitalization as an adverse event as a part of the composite outcome measure, or some additional adverse outcome, such as implantation of an automatic implantable cardioverter defibrillator, which did not count as an event in other studies. Notwithstanding, publication-based meta-analyses pool studies with diverse primary end point definitions that report one clinical outcome as an adverse event, resulting in a high level of heterogeneity and inconsistency between trials. This approach also leads to contradictory conclusions of the effect of cell therapy on mortality or combined or separate adverse events, with significant effects in 1 meta-analysis but not in another (Table 2).

It is not uncommon for different meta-analyses to have conflicting results. As with clinical trials that use different methodologies (eg, continuous end points versus dichotomous end points, different follow-up periods or imaging modalities), meta-analyses commonly have differences in their end points, outcome assessments, and conclusions. As long as the collection of studies or the methodologies of analyses are different, we can anticipate that results from the meta-analyses will vary. A difference in results is more likely when the overall effect size, the primum movens of the meta-analyses is small with large confidence intervals. An exception is the only IPD meta-analysis of the ACCRUE, which included a large number of patients using predefined clinical events for all studies. This translated into highly consistent estimates with low or no heterogeneity for clinical outcomes analyses. In addition, IPD collection allows time-to-event data to be generated for estimating time-dependent event-free survival, which is completely impossible in a publication-based meta-analysis.

Another exception is the Cochrane database analyses, which pooled studies with the same definitions for adverse outcome, or measurement of EF at the same time point using the same imaging tool.[5,11] Although this method seems to be the statistically most correct with the highest quality among publication-based meta-analyses, such an approach leads to the reduction in the number of patients, in particular, in the subgroups. It also might be responsible for some surprising results, such as a lower long-term (12–60 months) restenosis rate (2.7% in the bone marrow mononuclear cell group in 4 studies) than short-term (<12 months) restenosis rate (11.3% in the bone marrow mononuclear cell group) or a higher incidence of target vessel revascularization (11.9% in the bone marrow mononuclear cell group in 9 studies with <12-month follow-up and 14.3% in the bone marrow mononuclear cell group with long-term follow-up) than restenosis rate after cell therapy or control treatment.[11] Furthermore, the continuous updating of the Cochrane database to include more studies with more patients (similar to other

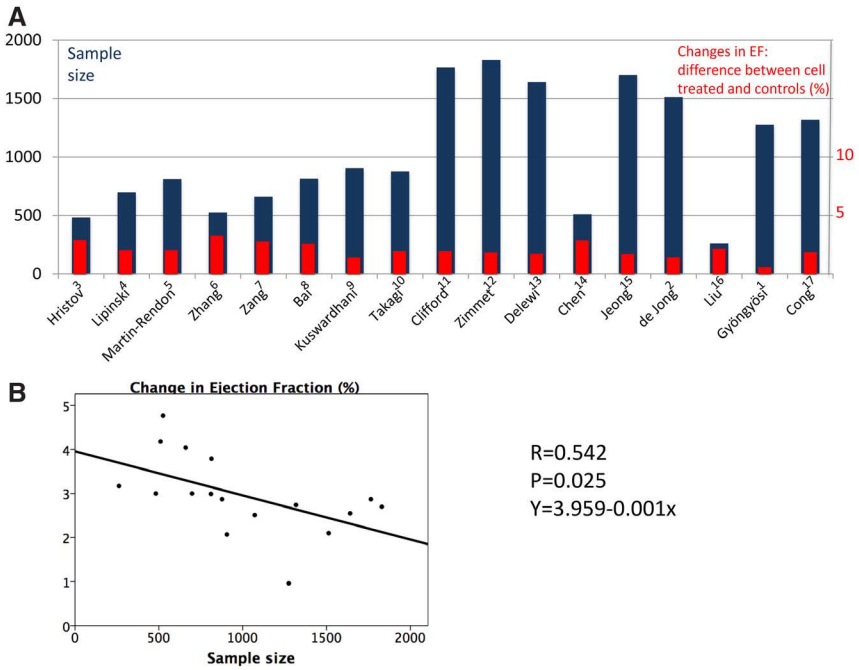

Figure 1. Association between the number of patients (sample size) and weighted mean difference in the left ventricular ejection fraction (EF) between cell-based treatment and controls in meta-analyses of intracoronary cell therapy in patients with recent acute myocardial infarction. **A**, Sample size (blue columns) and changes in EF from baseline to follow-up (differences between cell-treated and controls; red columns). **B**, Correlation between sample size and mean difference in EF between cell-based treatment and control groups.

meta-analyses) leads to some contrasting results compared with the previous version of the meta-analysis.[5,11] However, even if ACCRUE used prespecified dichotomous parameters, the imaging modalities for measuring the continuous parameter are different and may vary in any of the IPD-based databases, which is one major drawback of such data collection.

Heterogeneous Statements on the Results of Subgroup Analyses

One important but surprising finding of the ACCRUE IPD meta-analysis was the similar EF improvement in both cell-based treatment and controls in the subgroup of patients with low baseline EF. Some cell therapy trials[22,29,30] and meta-analyses[12–14]

Table 2. Different Results of Meta-Analyses Are Reporting Mortality or Combined or Separate Adverse Events

Cell Therapy for Cardiac Repair	No. of Studies	Sample Size	FUP, mo	Mortality	Combined Adverse Events	Separate Adverse Events Significant in Cell-Treated Group
Hristov et al[3]	5	482	6	nr	nr	
Lipinski et al[4]	10	698	6	Nonsignif.	Nonsignif.	Re-AMI lower
Martin-Rendon et al[5]	13	811	3–6	Nonsignif.	Nonsignif.	
Zhang et al[6]	6	525	5	nr	Nonsignif.	
Zhang et al[7]	7	660	6	Nonsignif.	Nonsignif.	
Bai et al[8]	10	814	6	nr	nr	
Kuswardhani et al[9]	10	906	4–60	Nonsignif.	nr	
Takagi and Umemoto[10]	15	877	nr	nr	nr	
Clifford et al[11]	33	1765	< or >12	Signif.	Nonsignif.	
Zimmet et al[12]	29	1830	3–6	Nonsignif.	Nonsignif.	TVR lower
Delewi et al[13]	16	1641	3–6	nr	Nr	
Chen et al[14]	5	510	nr	nr	Nonsignif.	
Jeong et al[15]	17	1072	3–6	nr	nr	
de Jong et al[2]	22	1513	6	Nonsignif.	Nonsignif.	
Liu et al[16]	8	262	6–24	Signif.	Nonsignif.	TVR higher
Gyöngyösi et al[1]	12	1275	12	Nonsignif.	Nonsignif.	
Cong et al[17]	17	1318	12	Nonsignif.	nr	

Gyöngyösi et al[1] Meta-Analysis of Cell-Based Cardiac Studies (ACCRUE) individual patient data-based meta-analysis in contrast with all other publication-based meta-analyses. Re-AMI indicates reinfarction; FUP, follow-up; nonsignif, no significant benefit of cell therapy; nr, not reported; signif., significant benefit of cell therapy; and TVR, target vessel revascularization

Table 3. Results of Subgroup Analyses in Different Meta-Analyses

Cell Therapy for Cardiac Repair	No. of Studies	Sample Size	Effect of Baseline EF on Increase in EF in Cell-Treated Group	Effect of Time From AMI to Cell Delivery on Increase in EF in Cell-Treated Group	Effect of no. of Delivered Cells on Increase in EF in Cell-Treated Group
Hristov et al[3]	5	482	nr	nr	nr
Lipinski et al[4]	10	698	Nonsignif.	Nonsignif.	Nonsignif.
Martin-Rendon et al[5]	13	811	nr	Signif.	signif.
Zhang et al[6]	6	525	nr	nr	nr
Zhang et al[7]	7	660	nr	Signif.	nr
Bai et al[8]	10	814	nr	nr	nr
Kuswardhani et al[9]	10	906	nr	nr	nr
Takagi and Umemoto[10]	15	877	nr	nr	nr
Clifford et al[11]	33	1765	nr	Signif.	Signif.
Zimmet et al[12]	29	1830	Signif.	Signif.	Signif.
Delewi et al[13]	16	1641	Signif.	Nonsignif.	Nonsignif.
Chen et al[14]	5	510	Signif.	nr	nr
Jeong et al[15]	17	1072	nr	nr	nr
de Jong et al[2]	22	1513	nr	nr	Nonsignif.
Liu et al[16]	8	262	nr	nr	nr
Gyöngyösi et al[1]	12	1275	Nonsignif.	Nonsignif.	Nonsignif.
Cong et al[17]	17	1318	nr	nr	nr

Gyöngyösi et al[1] Meta-Analysis of Cell-Based Cardiac Studies (ACCRUE) individual patient data-based meta-analysis in contrast with all other publication-based meta-analyses. AMI indicates acute myocardial infarction; EF, ejection fraction; Nonsignif., nonsignificant; nr, not reported; and Signif.; significant.

are in agreement that patients with lower EF benefit more from cell therapy than patients with higher baseline EF, in terms of a greater increase in the EF at follow-up. This is in contrast with the results of another study[31] and meta-analyses.[1,4] Conflicting statements describing the effect of time (time interval between STEMI and cell therapy/randomization) and the number of injected cells increase the uncertainty about the effect of cell therapy (Table 3). Nevertheless, an effect of a parameter on outcome may not be strongly convincing if significant in one meta-analysis but not in another.

Furthermore, as the EF increases continuously during the first year after STEMI under standardized treatment, a lower EF measured very early after STEMI attack is a priori associated with a greater increase in EF (Figure 2).[32] Resolution of the myocardial stunning in the immediate postinfarct period can dramatically improve the left ventricular EF. Thus, the timing of when the baseline EF is measured both in cell-treated and control patients is critical for the correct interpretation of the EF improvement. Accordingly, patients in the placebo group with lower EF demonstrated a greater increase in the EF during the follow-up in the ACCRUE. The changes in EF in the subgroups of cell-treated patients with baseline EF <50%, <45%, or <40% were 4.1±9.9%, 4.5±9.8%, or 5.0±9.7%, respectively; these values were similar to the controls classified into the same subgroup categories (3.5±9.0%, 3.8±9.0%, or 4.1±9.6%, respectively) in the ACCRUE.[1] Although patients with cell-based treatment with lower EF at baseline have a greater increase in the EF (Figure 2), this is also true for the control group. Both randomization arms received the standard medical therapy, with additional cell-based treatment in 1 group. However, the magnitude of the difference between the groups, which may be attributed to the cell therapy itself, was not significant.

The meta-analyses pooled studies that used different methods for measuring EF, except for the Cochrane database.[5,11] Measurement of left ventricular function using various methods results in various normal values and measurement errors. The methodological error of measuring left ventricular EF is 2.97% to 3.56% for MRI and ≤7.4% for echocardiography, and the absolute value of EF is lower if measured by radionuclide imaging.[33–35] In addition, the difference in EF between cell-based

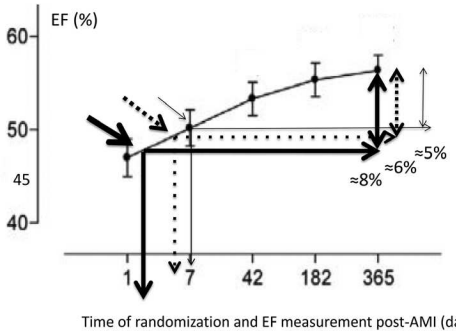

Figure 2. Increased ejection fraction (EF) under standard medical treatment for acute myocardial infarction (AMI). Note that the lower the baseline EF at randomization/cell treatment, the higher the increase in EF at the 1-year follow-up. Adapted from Engblom et al[32] with permission of the publisher. Copyright ©2009, Wolters Kluwer Health.

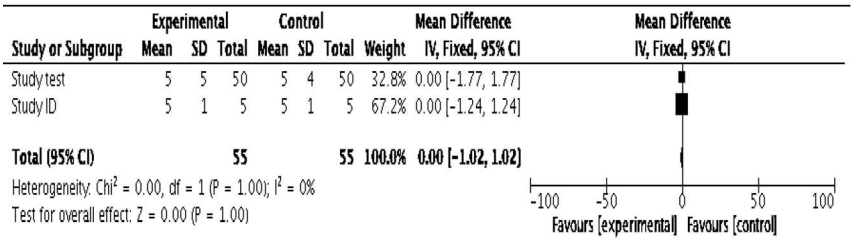

Figure 3. Schematic of a forest plot statistic for calculation of the mean difference in a continuous parameter between the treated and control groups. Note that a 10-fold larger study has less weight in the final results due to a larger SD. CI indicates confidence interval; and IV, inverse variance.

treatment and controls is always lower when MRI is used versus echocardiography or contrast ventriculography.[36] However, it is unclear whether a mean difference of 0.9% to 4% in the EF between cell therapy and controls is greater than the methodological error and represents a real, clinically relevant improvement.

Bias of Meta-Analyses

Data Collection Bias of Aggregate Data Versus Prespecified Outcome Collection in IPD

One of the major pitfalls of meta-analyses is collection bias related to the inclusion of clinically heterogeneous studies. Publication-based meta-analyses can include all studies but because of nonunique definitions of the parameters, they have high, nearly inacceptable heterogeneity between trials. In contrast, the IPD meta-analysis (ie, ACCRUE) used predefined end points; therefore, the heterogeneity and inconsistency is low, ≈0% for adverse events. The IPD approach allowed analysis of the data according to the intention-to-treat principle. However, the IPD meta-analysis results depend strongly on the choice of included studies (which is based on the availability of IPDs) and international cooperation between investigators. Thus, the inclusion of a majority of negative trials without the possibility of balanced inclusion of positive trials results in a negative outcome. The ACCRUE included 12 studies with 104 patients per group, in contrast with the nonparticipating 19 studies with a mean of 46 patients per group.[1] Participating in ACCRUE required an agreement between the principal investigators of the study and the ACCRUE data committee on the aim and objectives of the ACCRUE, and involvement should be approved by the institutional scientific and publication policy and local ethical committee. Furthermore, because of different definitions used in the original study and the ACCRUE database, unavoidable differences between the published summary and IPD may develop in regards to terms and the interpretation of the result. This is a vulnerable target for international critics and a major reason for not participating in an IPD-based meta-analysis.

The IPD-based meta-analysis focuses on the most important parameters and keeping the database as simple as possible; as a result, drawbacks of this approach include the omission of some surrogate outcome parameters and a lack of data on subjective measures. Publication-based meta-analyses can evaluate all published parameters, such as different follow-up times,[2,3,6,12] injected cell volume,[5,11] infarct size,[5,11] bone marrow aspiration in the control group,[15] different cell types,[5,11,16] details on cell preparation,[17] quality of life scores,[5] or any subjective or semiobjective parameter. Some of these data are evaluated even if they are only reported in a fraction of the collected trials. For example, myocardial infarct size decreased by 3.51% (P=0.004; n=240 patients) in the study of Martin-Rendon et al[5] and by 1.9% (not significant; n=670 patients) in the study of Clifford et al[11] if follow-up was <12 months,[11] but the improvement was 3.36% when studies with ≥12-month follow-up were selected (P=0.0021; n=353 patients in the bone marrow cell therapy groups compared with controls). Evaluating changes in the infarct size is particularly difficult because most of the studies did not assess baseline infarct size. Similarly, heterogeneous results have been published on changes in the wall motion score index: not significant if follow-up was <12 months (−0.06; P=0.17; n=747 patients) but significant in another meta-analysis (−0.06; P=0.002; n=793 patients), and with longer follow-up (≥12 months; −0.12; P=0.0042; n=279 patients; thus the statistics may be contradictory when including different studies.).[11,17] The incidences of cardiac arrhythmias were similar in subgroups of cell-treated and control patients.[5,6] As mentioned in the ACCRUE paper, even if such data were collected in IPD-based meta-analyses, data available for <50% of the patients may not represent the whole collective; therefore, these data were not assessed.

Using IPDs avoids data conflicts. In addition, the IPD-based meta-analysis using original data is protected from publication errors or from duplicate publications caused by diverse subgroup analyses. Yet, a major problem of IPD analysis remains the long and overwhelming effort needed for data collection and analysis if no financial support is available.

Analysis Bias

Meta-analyses that rely on published literature may report some inaccuracies in summarizing the results, as different studies provide data in various formats. An example of this is the statistical calculation of the benefit of cardiac cell therapy required for forest plotting for each of the control and cell treatment groups that includes (1) sample size, (2) mean changes from baseline to follow-up, and (3) the SD of these changes (Figure 3). However, if a study does not publish the changes in EF, but instead only the baseline and follow-up EF, the recalculation of the mean change is flawed because the mean change should include individuals who have evaluation at both baseline and follow-up. Thus, although this recalculation is based on widely accepted mathematical–statistical formulas,[37] it may result in a different mean±SD than the unpublished data available to the trial's investigators. Approximately half of the cell-based cardiac regeneration studies do not report arithmetic means and SDs for the changes in continuous outcome parameters, such as EF. Consequently, virtual recalculated mean±SD of some studies are used in different meta-analyses (Table 4)[2,20] (Online References X–XIX), which enter different numeric data for

Table 4. Examples of Reported Changes (Mean±SD) of Left Ventricular EF From Baseline to Follow-Up in the Original Publications (†), Compared With the Recalculated Values in the Publications of Jeevananthan et al[20] (‡) and de Jong et al[2] (§)

	Reported Changes in EF, %	Reported Changes in EF, %	Calculated Changes in EF, %	Calculated Changes in EF, %	Calculated Changes in EF, %	Calculated Changes in EF, %	Calculated Changes in EF, %	Calculated Changes in EF, %
	Original Publication, Mean±SD	Original Publication, Mean±SD	Jeevananthan et al,[20] Mean±SD	Jeevananthan et al,[20] Mean±SD	Jeevananthan et al[20]	de Jong et al,[2] Mean±SD	de Jong et al,[2] Mean±SD	de Jong et al[2]
Intracoronary Cell Injection Study	Cell Treated	Controls	Cell Treated	Controls	Weight of Study in Forest Plot	Cell Treated	Controls	Weight of Study in Forest Plot
Ge (Online Reference X	4.8+*	−1.9+†	4.8±9.6*‡	−1.9±5.9‡	1.3‡	4.8±5.2*§	3.5±1.9§	4.8§
Penicka (Online Reference XI)	15.4+*	20.5+†	15.4±5.5*‡	20.5±4.6‡	2.1‡	6±5*§	8±4.8§	4.4§
Meluzin (Online Reference XII)	3±1 and 5±1++*	2±1†	4.0±4.7*‡	2.0±4.7‡	2.6‡	5±6.6*§	0±8.9§	4.1§
Nogueira (Online Reference XIII)	nr*	nr†	6.9±6.2*‡	2±11‡	0.9‡	6.7±5.5*§	2±11.5§	1.7§
Plewka (Online Reference XIV)	10±9*	5±8†	9±7*‡	5±3.6§	2.5‡	9±5.8*§	5±4.9§	5.2§
Cao (Online Reference XV)	nr*	nr†	11.5±3.2*‡	7.9±3.4‡	2.9‡	9.4±1.8*§	7.1±2.6§	6.5§
Yao (Online Reference XVI)	7.2±1.6 and 11.7±2.6++*	2.9±2†	9.8±3.5*‡	3.0±2.3‡	2.8‡	6.2±2.4*§	2.2±1.8§	6.3§
Grajek (Online Reference XVII)	nr*	nr†	−3.4±5.9*‡	−6.4±7.9‡	1.9‡	−2.5±5.6*§	0±7.8§	4.0§
Piepoli (Online Reference XVIII)	13.1±1.9*	5.3±2†	9.5±2.6*‡	3.5±2.9‡	2.8‡	8.4±9.2*§	2.2±12.6§	2.5§
Hirsch (Online Reference XIX)	3.8±7.4 and 4.2±6.2++*	4.0±5.8†	…	…	…	3.8±7.4*§	5.2±5.8§	5.7§

Note the disparities between the original publications and recalculated values of both meta-analyses. +SD of mean not reported, ++ 2 different cell-treatment arms; nr, mean changes ± SD not reported (only baseline and follow-up absolute values are reported). Weight of the here selected (not all) studies from total 36 studies in the meta-analysis of Jeevanantham et al[20] and 22 studies in the meta-analysis of de Jong et al.[2] EF indicates ejection fraction; and nr, not reported.

the same study into the forest plot statistics and decrease precision in their overall estimate. The SDs are pivotal for computing the statistical weights of the studies; therefore, such an approach can lead to biased conclusions, not assigning a real weight to the study, and ultimately masking the true statistical effect (Figure 3). Moreover, summary data are often presented for the entire study population, even if paired baseline-follow-up data are not available for all patients. In contrast to these approaches, the IPD-based meta-analysis (such as the ACCRUE) uses the original data, with the ultimate benefit of not needing virtual data calculation. Accordingly, no difference was found between the IPD-calculated changes in the mean and SD and the values of the original studies if the study published these parameters.

Some differences between the meta-analysis results can also be attributed to errors in the individual publications and meta-analyses. However, the current review does not address the discrepancies found in the individual studies or meta-analyses. The aim of presentation of data in Table 4 is to show some examples of how different the numbers entered into the decisive forest plot statistics can be if they are recalculated.

Summary of the Advantages and Disadvantages of Different Types of Meta-Analyses of Cell-Based Cardiac Studies

Currently, several types of meta-analyses have been conducted to analyze the effect of cell therapy in ischemic heart disease (Table 5). There are different high-quality meta-analyses with

Table 5. Types of Meta-Analyses in Cell-Based Cardiac Regeneration

Meta-Analysis	Example	Type	Analysis Type	Advantage	Disadvantage
Pooling all studies	Jeevananthan et al[20]	RCT-Pb	All studies analyzed as one collective	Large sample size	Large heterogeneity, missing data recalculated
Pooling certain studies with predefined inclusion criteria	Clifford et al[11]	RCT-Pb	Different studies in subgroups	Large sample size, but lower number of patients in subgroups	Less heterogeneity, missing data recalculated
Pooling certain studies with predefined inclusion criteria	Delewi et al[13]	RCT-Pb, summary of mean of subgroups	Different studies in subgroups	Large sample size, but lower number of patients in subgroups	Less heterogeneity, missing data recalculated
Pooling certain studies with predefined inclusion criteria	Gyöngyösi et al[1]	RCT-IPD	All patients and studies analyzed as one collective	Low heterogeneity, original data in database	Lower number of patients and studies

IPD indicates individual patient data based; Pb, publication based; and RCT, randomized controlled studies.

specific aims and outcome measures, delivering different messages, and all have their advantages and disadvantages regarding the differences in analysis methodology, bias in data collection and study inclusion. All individual studies included ≤204 patients, so respective meta-analyses must pool small- and medium-sized clinical trials with nonuniform designs, cell types, delivery modes, and follow-up times. Consequently, there is a lack of homogeneity. In addition, the trials used cell therapy at different times after the ischemic event and had diverse inclusion or exclusion criteria. Even if the collection of IPD for meta-analyses is regarded as the gold standard,[37] no meta- analysis approach can replace randomized multicenter blinded studies.

Pitfalls of Evidence-Based Medicine: Negative Outcome of a Randomized Clinical Study Based on Positive Meta-Analysis Results

It has already been acknowledged that the results of meta-analyses can differ from subsequent large randomized clinical trials.[38,39] The quality of publication-based meta-analyses depends on the quality, outcome assessment, and statistical report of the included clinical studies. Because of the variable precision of meta-analyses, the observed effect could be overestimated. Positive meta-analysis results can pave the way to initiating a large randomized clinical study with a neutral or negative outcome, as has been observed several times in medical literature and practice.[38,39]

Large randomized trials are considered the gold standard with the highest quality level I evidence for application of the study results in clinical practice based on the evidence-based medicine grading system. Importantly, the prespecified data collected in IPD-based meta-analyses (eg, ACCRUE) allow the results to truly reflect the original data, as well as pool them in a database in similar form as clinical trial case reports. Thus, IPD collection may be considered a novel prospective multicenter large randomized clinical trial and the IPD meta-analyses as evidence-based medicine.

Conclusions

The IPD meta-analysis is currently considered the gold standard for meta-analyses assessing the impact of a treatment on clinical outcomes, especially in the case of small- and medium-sized clinical cardiac regeneration studies. An IPD approach, such as the ACCRUE, permits data verification and allows adjustment for the same variables across studies. When dealing with cardiovascular outcomes, this approach generates time-to-event data for estimating survival, can explore heterogeneity at the patient level, and allows subgroup analyses. Using prespecified terms and conditions, the database is similar to that of a prospective multicenter randomized clinical trial with similar statistical assessment modalities combined with standardized approaches to evaluating meta-analyses.

Although data based on individual patients, rather than summary measures across patients, are preferable, these data are commonly unavailable. The IPD analyses rely on the data being available from studies. The IPD database is kept simple; therefore, a meta-analysis cannot evaluate some surrogate parameters if data are not gathered or factors are not available, such as different quality of life assessment scores.

The difficulties of the standard meta-analysis approaches have been reviewed here. Each has a place in the analysis of data when pivotal clinical trials are not available and each sheds light on the magnitude of the treatment effect in a complex healthcare field.

Appendix

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Disclosures

None.

References

1. Gyöngyösi M, Wojakowski W, Lemarchand P, et al; ACCRUE Investigators. Meta-Analysis of Cell-based CaRdiac stUdiEs (ACCRUE) in patients with acute myocardial infarction based on individual patient data. *Circ Res*. 2015;116:1346–1360. doi: 10.1161/CIRCRESAHA.116.304346.
2. de Jong R, Houtgraaf JH, Samiei S, Boersma E, Duckers HJ. Intracoronary stem cell infusion after acute myocardial infarction: a meta-analysis and update on clinical trials. *Circ Cardiovasc Interv*. 2014;7:156–167. doi: 10.1161/CIRCINTERVENTIONS.113.001009.
3. Hristov M, Heussen N, Schober A, Weber C. Intracoronary infusion of autologous bone marrow cells and left ventricular function after acute myocardial infarction: a meta-analysis. *J Cell Mol Med*. 2006;10:727–733.
4. Lipinski MJ, Biondi-Zoccai GG, Abbate A, Khianey R, Sheiban I, Bartunek J, Vanderheyden M, Kim HS, Kang HJ, Strauer BE, Vetrovec GW. Impact of intracoronary cell therapy on left ventricular function in the setting of acute myocardial infarction: a collaborative systematic review and meta-analysis of controlled clinical trials. *J Am Coll Cardiol*. 2007;50:1761–1767. doi: 10.1016/j.jacc.2007.07.041.
5. Martin-Rendon E, Brunskill SJ, Hyde CJ, Stanworth SJ, Mathur A, Watt SM. Autologous bone marrow stem cells to treat acute myocardial infarction: a systematic review. *Eur Heart J*. 2008;29:1807–1818. doi: 10.1093/eurheartj/ehn220.
6. Zhang SN, Sun AJ, Ge JB, Yao K, Huang ZY, Wang KQ, Zou YZ. Intracoronary autologous bone marrow stem cells transfer for patients with acute myocardial infarction: a meta-analysis of randomised controlled trials. *Int J Cardiol*. 2009;136:178–185. doi: 10.1016/j.ijcard.2008.04.071.

7. Zhang S, Sun A, Xu D, Yao K, Huang Z, Jin H, Wang K, Zou Y, Ge J. Impact of timing on efficacy and safetyof intracoronary autologous bone marrow stem cells transplantation in acute myocardial infarction: a pooled subgroup analysis of randomized controlled trials. *Clin Cardiol*. 2009;32:458–466. doi: 10.1002/clc.20575.
8. Bai Y, Sun T, Ye P. Age, gender and diabetic status are associated with effects of bone marrow cell therapy on recovery of left ventricular function after acute myocardial infarction: a systematic review and meta-analysis. *Ageing Res Rev*. 2010;9:418–423. doi: 10.1016/j.arr.2010.05.001.
9. Kuswardhani RA, Soejitno A. Bone marrow-derived stem cells as an adjunctive treatment for acute myocardial infarction: a systematic review and meta-analysis. *Acta Med Indones*. 2011;43:168–177.
10. Takagi H, Umemoto T. Intracoronary stem cell injection improves left ventricular remodeling after acute myocardial infarction: an updated meta-analysis of randomized trials. *Int J Cardiol*. 2011;151:226–228. doi: 10.1016/j.ijcard.2011.05.084.
11. Clifford DM, Fisher SA, Brunskill SJ, Doree C, Mathur A, Watt S, Martin-Rendon E. Stem cell treatment for acute myocardial infarction. *Cochrane Database Syst Rev*. 2012;2:CD006536. doi: 10.1002/14651858.CD006536.pub3.
12. Zimmet H, Porapakkham P, Porapakkham P, Sata Y, Haas SJ, Itescu S, Forbes A, Krum H. Short- and long-term outcomes of intracoronary and endogenously mobilized bone marrow stem cells in the treatment of ST-segment elevation myocardial infarction: a meta-analysis of randomized control trials. *Eur J Heart Fail*. 2012;14:91–105. doi: 10.1093/eurjhf/hfr148.
13. Delewi R, Hirsch A, Tijssen JG, et al. Impact of intracoronary bone marrow cell therapy on left ventricular function in the setting of ST-segment elevation myocardial infarction: a collaborative meta-analysis. *Eur Heart J*. 2014;35:989–998. doi: 10.1093/eurheartj/eht372.
14. Chen L, Tong JY, Jin H, Ren XM, Jin H, Wang QJ, Ma GS. Long-term effects of bone marrow-derived cells transplantation in patients with acute myocardial infarction: a meta-analysis. *Chin Med J (Engl)*. 2013;126:353–360.
15. Jeong H, Yim HW, Cho Y, Park HJ, Jeong S, Kim HB, Hong W, Kim H. The effect of rigorous study design in the research of autologous bone marrow-derived mononuclear cell transfer in patients with acute myocardial infarction. *Stem Cell Res Ther*. 2013;4:82. doi: 10.1186/scrt233.
16. Liu B, Duan CY, Luo CF, Ou CW, Sun K, Wu ZY, Huang H, Cheng CF, Li YP, Chen MS. Effectiveness and safety of selected bone marrow stem cells on left ventricular function in patients with acute myocardial infarction: a meta-analysis of randomized controlled trials. *Int J Cardiol*. 2014;177:764–770. doi: 10.1016/j.ijcard.2014.11.005.
17. Cong XQ, Li Y, Zhao X, Dai YJ, Liu Y. Short-term effect of autologous bone marrow stem cells to treat acute myocardial infarction: a meta-analysis of randomized controlled clinical trials. *J Cardiovasc Transl Res*. 2015;8:221–231. doi: 10.1007/s12265-015-9621-9.
18. Ye Z, Zhang BL, Zhao XX, Qin YW, Wu H, Cao J, Zhang JL, Hu JQ, Zheng X, Xu RL. Intracoronary infusion of bone marrow-derived mononuclear cells contributes to longstanding improvements of left ventricular performance and remodelling after acute myocardial infarction: a meta-analysis. *Heart Lung Circ*. 2012;21:725–733. doi: 10.1016/j.hlc.2012.06.024.
19. Abdel-Latif A, Bolli R, Tleyjeh IM, Montori VM, Perin EC, Hornung CA, Zuba-Surma EK, Al-Mallah M, Dawn B. Adult bone marrow-derived cells for cardiac repair: a systematic review and meta-analysis. *Arch Intern Med*. 2007;167:989–997. doi: 10.1001/archinte.167.10.989.
20. Jeevanantham V, Butler M, Saad A, Abdel-Latif A, Zuba-Surma EK, Dawn B. Adult bone marrow cell therapy improves survival and induces long-term improvement in cardiac parameters: a systematic review and meta-analysis. *Circulation*. 2012;126:551–568. doi: 10.1161/CIRCULATIONAHA.111.086074.
21. Afzal MR, Samanta A, Shah ZI, Jeevanantham V, Abdel-Latif A, Zuba-Surma EK, Dawn B. Adult bone marrow cell therapy for ischemic heart disease: evidence and insights from randomized controlled trials. *Circ Res*. 2015;117:558–575. doi: 10.1161/CIRCRESAHA.114.304792.
22. Tendera M, Wojakowski W, Ruzyłło W, Chojnowska L, Kepka C, Tracz W, Musiałek P, Piwowarska W, Nessler J, Buszman P, Grajek S, Breborowicz P, Majka M, Ratajczak MZ; REGENT Investigators. Intracoronary infusion of bone marrow-derived selected CD34+CXCR4+ cells and non-selected mononuclear cells in patients with acute STEMI and reduced left ventricular ejection fraction: results of randomized, multicentre Myocardial Regeneration by Intracoronary Infusion of Selected Population of Stem Cells in Acute Myocardial Infarction (REGENT) Trial. *Eur Heart J*. 2009;30:1313–1321. doi: 10.1093/eurheartj/ehp073.
23. Traverse JH, Henry TD, Ellis SG, et al; Cardiovascular Cell Therapy ResearchNetwork. Effect of intracoronary delivery of autologous bone marrow mononuclear cells 2 to 3 weeks following acute myocardial infarction on left ventricular function: the LateTIME randomized trial. *JAMA*. 2011;306:2110–2119. doi: 10.1001/jama.2011.1670.
24. Traverse JH, Henry TD, Pepine CJ, et al; Cardiovascular Cell Therapy Research Network (CCTRN). Effect of the use and timing of bone marrow mononuclear cell delivery on left ventricular function after acute myocardial infarction: the TIME randomized trial. *JAMA*. 2012;308:2380–2389. doi: 10.1001/jama.2012.28726.
25. Sürder D, Manka R, Lo Cicero V, et al. Intracoronary injection of bone marrow-derived mononuclear cells early or late after acute myocardial infarction: effects on global left ventricular function. *Circulation*. 2013;127:1968–1979. doi: 10.1161/CIRCULATIONAHA.112.001035.
26. Makkar RR, Smith RR, Cheng K, Malliaras K, Thomson LE, Berman D, Czer LS, Marbán L, Mendizabal A, Johnston PV, Russell SD, Schuleri KH, Lardo AC, Gerstenblith G, Marbán E. Intracoronary cardiosphere-derived cells for heart regeneration after myocardial infarction (CADUCEUS): a prospective, randomised phase 1 trial. *Lancet*. 2012;379:895–904. doi: 10.1016/S0140-6736(12)60195-0.
27. Wöhrle J, Merkle N, Mailänder V, Nusser T, Schauwecker P, von Scheidt F, Schwarz K, Bommer M, Wiesneth M, Schrezenmeier H, Hombach V. Results of intracoronary stem cell therapy after acute myocardial infarction. *Am J Cardiol*. 2010;105:804–812. doi: 10.1016/j.amjcard.2009.10.060.
28. Andrade C. Signal-to-noise ratio, variability, and their relevance in clinical trials. *J Clin Psychiatry*. 2013;74:479–481. doi: 10.4088/JCP.13f08475.
29. Schächinger V, Erbs S, Elsässer A, Haberbosch W, Hambrecht R, Hölschermann H, Yu J, Corti R, Mathey DG, Hamm CW, Süselbeck T, Assmus B, Tonn T, Dimmeler S, Zeiher AM; REPAIR-AMI Investigators. Intracoronary bone marrow-derived progenitor cells in acute myocardial infarction. *N Engl J Med*. 2006;355:1210–1221. doi: 10.1056/NEJMoa060186.
30. Miettinen JA, Ylitalo K, Hedberg P, et al. Determinants of functional recovery after myocardial infarction of patients treated with bone marrow-derived stem cells after thrombolytic therapy. *Heart*. 2010;96:362–367. doi: 10.1136/hrt.2009.171694.
31. Roncalli J, Mouquet F, Piot C, et al. Intracoronary autologous mononucleated bone marrow cell infusion for acute myocardial infarction: results of the randomized multicenter BONAMI trial. *Eur Heart J*. 2011;32:1748–1757. doi: 10.1093/eurheartj/ehq455.
32. Engblom H, Hedström E, Heiberg E, Wagner GS, Pahlm O, Arheden H. Rapid initial reduction of hyperenhanced myocardium after reperfused first myocardial infarction suggests recovery of the peri-infarction zone: one-year follow-up by MRI. *Circ Cardiovasc Imaging*. 2009;2:47–55. doi: 10.1161/CIRCIMAGING.108.802199.
33. Danilouchkine MG, Westenberg JJ, de Roos A, Reiber JH, Lelieveldt BP. Operator induced variability in cardiovascular MR: left ventricular measurements and their reproducibility. *J Cardiovasc Magn Reson*. 2005;7:447–457.
34. Chukwu EO, Barasch E, Mihalatos DG, Katz A, Lachmann J, Han J, Reichek N, Gopal AS. Relative importance of errors in left ventricular quantitation by two-dimensional echocardiography: insights from three-dimensional echocardiography and cardiac magnetic resonance imaging. *J Am Soc Echocardiogr*. 2008;21:990–997. doi: 10.1016/j.echo.2008.07.009.
35. Schaefer WM, Lipke CS, Standke D, Kühl HP, Nowak B, Kaiser HJ, Koch KC, Buell U. Quantification of left ventricular volumes and ejection fraction from gated 99mTc-MIBI SPECT: MRI validation and comparison of the Emory Cardiac Tool Box with QGS and 4D-MSPECT. *J Nucl Med*. 2005;46:1256–1263.
36. Simari RD, Pepine CJ, Traverse JH, Henry TD, Bolli R, Spoon DB, Yeh E, Hare JM, Schulman IH, Anderson RD, Lambert C, Sayre SL, Taylor DA, Ebert RF, Moyé LA. Bone marrow mononuclear cell therapy for acute myocardial infarction: a perspective from the cardiovascular cell therapy research network. *Circ Res*. 2014;114:1564–1568. doi: 10.1161/CIRCRESAHA.114.303720.
37. Higgins JPT, Green S, eds. Cochrane Handbook for Systematic Reviews of Interventions 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. www.cochrane-handbook.org.
38. LeLorier J, Grégoire G, Benhaddad A, Lapierre J, Derderian F. Discrepancies between meta-analyses and subsequent large randomized, controlled trials. *N Engl J Med*. 1997;337:536–542. doi: 10.1056/NEJM199708213370806.
39. Shibata MC. What is wrong with meta-analysis? The importance of clinical heterogeneity in myocardial regeneration research. *Int J Clin Pract*. 2013;67:1081–1085. doi: 10.1111/ijcp.12232.

Response to Gyöngyösi, Wojakowski, Navarese, Moyé, and the ACCRUE Investigators

Enca Martin-Rendon

These 2 controversy articles attempt to explain why meta-analyses on cardiac cell-based regenerative studies report differing results. They provide a comprehensive review of the literature in the field at the present time. I think controversies in any field could have a very positive outcome, and I sincerely hope that this is the case for cell therapies in cardiac regeneration.

Noticeably, most of the controversies in the field stems from the lack of available data from a large, randomized, multicenter, blinded clinical trial and the substantial heterogeneity among clinical and meta-analytical studies. However, no meta-analysis is a replacement for that trial and as for any surrogate; one has to be mindful of its limitations and the fact that a meta-analytical finding may not always predict the results of a larger trial accurately.

I agree with the authors of the companion article that individual patient data meta-analyses can translate into reducing heterogeneity for clinical outcome measures and allow time-to-event data to be generated. Although the time and effort required and the financial costs of conducting an individual patient data meta-analysis can reduce their applicability in some cases. Here is where trial meta-analyses have their relevance. I have to emphasize that most established scientific knowledge is supported by a convergence of evidence. Interestingly, emerging evidence provided by qualitative (1) and quantitative (2, 3) assessment of cardiac cell-based regenerative studies suggests that patients who have had a recent myocardial infarction may not benefit from cell-based therapies over standard medical care. The question is whether other patients may benefit from these treatments. The Meta-Analysis of Cell-Based Cardiac Studies (ACCRUE) consortium has paved the way to encourage more international cooperation in this field. It has open the doors to more controversies that hopefully will stimulate more passionate debate and generate new work, whether is to conduct larger trials or to embark on more individual patient data studies. International cooperation will be needed in both cases.

I have been able to contribute to this miniseries because of the generosity of Professor Mariann Gyöngyösi, on behalf of the ACCRUE consortium, who suggested my name to the *Circulation Research* editorial team. I would also like to take this opportunity to thank all scientists and clinicians who have worked with me over the years evaluating clinical data and to all investigators who shared their unpublished data with us. Without them, the support of the Systematic Review Initiative and the Cochrane Heart Group, my work would not have been possible.

1. Traverse JH, Henry TD, Moye LA. Is the measurement of left ventricular ejection fraction the proper end point for cell therapy trials? An analysis of the effect of bone marrow mononuclear stem cell administration on left ventricular ejection fraction after ST-segment elevation myocardial infarction when evaluated by cardiac magnetic resonance imaging. *Am Heart J*. 2011;162:671–677. doi: 10.1016/j.ahj.2011.06.019.
2. Fisher SA, Zhang H, Doree C, Mathur A, Martin-Rendon E. Stem cell treatment for acute myocardial infarction. *Cochrane Database Syst Rev*. 2015;Sep 30;9:CD006536. doi: 10.1002/14651858.CD006536.pub4.
3. Gyöngyösi M, Wojakowski W, Lemarchand P, Lunde K, Tendera M, Bartunek J, Marban E, Assmus B, Henry TD, Traverse JH, Moyé LA, Sürder D, Corti R, Huikuri H, Miettinen J, Wöhrle J, Obradovic S, Roncalli J, Malliaras K, Pokushalov E, Romanov A, Kastrup J, Bergmann MW, Atsma DE, Diederichsen A, Edes I, Benedek I, Benedek T, Pejkov H, Nyolczas N, Pavo N, Bergler-Klein J, Pavo IJ, Sylven C, Berti S, Navarese EP, Maurer G; ACCRUE Investigators. Meta-Analysis of Cell-based CaRdiac stUdiEs (ACCRUE) in patients with acute myocardial infarction based on individual patient data. *Circ Res*. 2015;116:1346–1360. doi: 10.1161/CIRCRESAHA.116.304346.

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Meta-Analyses of Human Cell-Based Cardiac Regeneration Therapies: Controversies in Meta-Analyses Results on Cardiac Cell-Based Regenerative Studies

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Online Table I. List of meta-analyses assessing randomized controlled trials and included patients with chronic ischemic heart disease

Cell therapy for iCMP	Year	Type of MA	Nr of studies	Sample size	Diagnosis	Cell delivery route	FUP (months)	Mortality	Combined adverse events	Changes in EDV (mL)	Changes in ESV (mL)	Changes in EF (%)	Baseline EF effect on EF improve-ment	Changes in EF if MRI used
Xiao[S1]	2014	RCT	20	784	iCMP	with/without PCI/CABG	3-12	if no additional revasc., signif.	non-signif	-7.85*	-9.75*	3.22*	signif	nr
Kandala [S2]	2013	RCT	10	519	iCMP	ic/im percut/ im CABG	3-18	signif	nr	-16.71*	-20.64*	4.48*	signif	signif
Zhu [S3]	2015	RCT	11	635	iCMP	im percut/CABG	6-12	signif	nr	-4.73	-9.67*	2.57*	non-signif	nr
Fischer [S4]	2013	RCT	9	649	iCMP	ic/im percut/ im CABG	6-12	signif	nr	nr	nr	3.47*	nr	nr
Tian[S5]	2014	RCT	11	492	iCMP	im percut/CABG	3-12	nr	nr	-7.82	-10.66*	4.91*	non-signif	non-signif

* $p<0.05$

iCMP indicates ischemic cardiomyopathy; MA, meta-analysis; Nr, number; FUP, follow-up; EDV, end-diastolic volume; ESV, end-systolic volume; EF, ejection fraction; MRI, magnetic resonance imaging; RCT, randomized controlled trial; PCI, percutaneous coronary intervention; CABG, coronary artery bypass surgery; ic, intracoronary; im, intramyocardial; percut, percutaneous; revasc, revascularization; signif, significant; nr, not reported; non-signif, non-significant.

Online Table II. List of meta-analyses assessing randomized and cohort trials and included patients with recent acute myocardial infarction and chronic ischemic heart disease

Cell therapy for iCMP/AMI	Year	Type of MA	Nr of studies	Sample size	Diagnosis	Cell delivery route	FUP (months)	Mortality	Combined adverse events	Changes in EDV (mL)	Changes in ESV (mL)	Changes in EF (%)	Baseline EF effect on EF improve-ment	Changes in EF if MRI used
Abdel-Latif[S6]	2007	RCT+ cohort studies	18	999	AMI, iCMP	ic/im percut, im CABG	3-18	nr	nr	-1.92	-4.8*	3.66*	nr	nr
Jeevanantham[S7]	2012	RCT+ cohort studies	50	2625	AMI, iCMP	ic/im percut, im CABG	3-60	signif	nr	-5.23*	-8.91*	3.96*	non-signif	non-signif
Sadat[S8]	2014	RCT+ cohort studies	32	2406	AMI, iCMP	ic/im percut	3-61	nr	nr	nr	nr	4.6±0.7*	non-signif	nr
Afzal[S9]	2015	RCT+ cohort studies	48	2602	AMI, IHD, CIHD	ic/im percut, im CABG	3-48	non-signif	signif	-2.26	-6.37*	2.92*	signif	nr

* $p<0.05$

iCMP indicates ischemic cardiomyopathy; AMI, acute myocardial infarction; MA, meta-analysis; Nr, number; FUP, follow-up; EDV, end-diastolic volume; ESV, end-systolic volume; EF, ejection fraction; MRI, magnetic resonance imaging; RCT, randomized controlled trial; IHD, ischemic heart disease; CIHD, chronic ischemic heart disease; CABG, coronary artery bypass surgery; ic, intracoronary; im, intramyocardial; percut, percutaneous; signif, significant; nr, not reported; non-signif, non-significant.

Supplemental References

S1. Xiao C, Zhou S, Liu Y, Hu H. Efficacy and safety of bone marrow cell transplantation for chronic ischemic heart disease: a meta-analysis. *Med Sci Monit.* 2014;20:1768-1777.

S2. Kandala J, Upadhyay GA, Pokushalov E, Wu S, Drachman DE, Singh JP. Meta-analysis of stem cell therapy in chronic ischemic cardiomyopathy. *Am J Cardiol.* 2013;112:217-225.

S3. Zhu K, Li J, Wang Y, Luo J, Zhang W, Guo C, Lai H, Wang C. Intramyocardial Autologous Bone Marrow-derived Stem Cells Injection for Ischemic Heart Disease Ineligible for Revascularization: A Systematic Review and Meta-analysis. *Arch Med Res.* 2015;46:286- 295.

S4. Fisher SA, Dorée C, Brunskill SJ, Mathur A, Martin-Rendon E. Bone Marrow Stem Cell Treatment for Ischemic Heart Disease in Patients with No Option of Revascularization: A Systematic Review and Meta-Analysis. *PLoS One*. 2013;8:e64669.

S5. Tian T, Chen B, Xiao Y, Yang K, Zhou X. Intramyocardial autologous bone marrow cell transplantation for ischemic heart disease: a systematic review and meta-analysis of randomized controlled trials. *Atherosclerosis*. 2014;233:485-492.

S6. Abdel-Latif A, Bolli R, Tleyjeh IM, Montori VM, Perin EC, Hornung CA, Zuba-Surma EK, Al-Mallah M, Dawn B. Adult bone marrow-derived cells for cardiac repair: a systematic review and meta-analysis. *Arch Intern Med*. 2007;167:989-997.

S7. Jeevanantham V, Butler M, Saad A, Abdel-Latif A, Zuba-Surma EK, Dawn B. Adult bone marrow cell therapy improves survival and induces long-term improvement in cardiac parameters: a systematic review and meta-analysis. *Circulation.* 2012;126:551-556.

S8. Sadat K, Ather S, Aljaroudi W, Heo J, Iskandrian AE, Hage FG. The effect of bone marrow mononuclear stem cell therapy on left ventricular function and myocardial perfusion. *J Nucl Cardiol.* 2014;21:351-367.

S9. Afzal MR, Samanta A, Shah ZI, Jeevanantham V, Abdel-Latif A, Zuba-Surma EK, Dawn B. Adult Bone Marrow Cell Therapy for Ischemic Heart Disease: Evidence and Insights from Randomized Controlled Trials. *Circ Res.* 2015;117:558-575.

S10. Ge J, Li Y, Qian J, Shi J, Wang Q, Niu Y, Fan B, Liu X, Zhang S, Sun A, Zou Y. Efficacy of emergent transcatheter transplantation of stem cells for treatment of acute myocardial infarction (TCT-STAMI). *Heart*. 2006;92:1764-1767.

S11. Penicka M, Horak J, Kobylka P, Pytlik R, Kozak T, Belohlavek O, Lang O, Skalicka H, Simek S, Palecek T, Linhart A, Aschermann M, Widimsky P. Intracoronary injection of autologous bone marrow-derived mononuclear cells in patients with large anterior acute myocardial infarction:

a prematurely terminated randomized study. *J Am Coll Cardiol.* 2007;49:2373–2374.

S12. Meluzin J, Mayer J, Groch L, et al. Autologous transplantation of mononuclear bone marrow cells in patients with acute myocardial infarction: the effect of the dose of transplanted cells on myocardial function. *Am Heart J.* 2006;152:975.e9–975.e15.

S13. Nogueira FB, Silva SA, Haddad AF, Peixoto CM, Carvalho RM, Tuche FA, Soares VE, Sousa AL, Rabischoffsky A, Mesquita CT, Borojevic R, Dohmann HF. Systolic function of patients with myocardial infarction undergoing autologous bone marrow transplantation. *Arq Bras Cardiol.* 2009;93:374-379.

S14. Plewka M, Krzemińska-Pakuła M, Lipiec P, Peruga JZ, Jezewski T, Kidawa M, Wierzbowska-Drabik K, Korycka A, Robak T, Kasprzak JD. Effect of intracoronary injection of mononuclear bone marrow stem cells on left ventricular function in patients with acute myocardial infarction. *Am J Cardiol.* 2009;104:1336-1342.

S15. Cao F, Sun D, Li C, Narsinh K, Zhao L, Li X, Feng X, Zhang J, Duan Y, Wang J, Liu D, Wang H. Long-term myocardial functional improvement after autologous bone marrow mononuclear cells transplantation in patients with ST-segment elevation myocardial infarction: 4 years follow-up. *Eur Heart J*. 2009;30:1986-1994.

S16. Yao K, Huang R, Sun A, Qian J, Liu X, Ge L, Zhang Y, Zhang S, Niu Y, Wang Q, Zou Y, Ge J. Repeated autologous bone marrow mononuclear cell therapy in patients with large myocardial infarction. *Eur J Heart Fail*. 2009;11:691-698.

S17. Grajek S, Popiel M, Gil L, Breborowicz P, Lesiak M, Czepczyński R, Sawiński K, Straburzyńska-Migaj E, Araszkiewicz A, Czyz A, Kozłowska-Skrzypczak M, Komarnicki M. Influence of bone marrow stem cells on left ventricle perfusion and ejection fraction in patients with acute myocardial infarction of anterior wall: randomized clinical trial: impact of bone marrow stem cell intracoronary infusion on improvement of microcirculation. *Eur Heart J.* 2010;31:691-702.

S18. Piepoli MF, Vallisa D, Arbasi M, Cavanna L, Cerri L, Mori M, Passerini F, Tommasi L, Rossi A, Capucci A; Cardiac Study Group. Bone marrow cell transplantation improves cardiac, autonomic, and functional indexes in acute anterior myocardial infarction patients (Cardiac Study). *Eur J Heart Fail.* 2010;12:172-180.

S19. Hirsch A, Nijveldt R, van der Vleuten PA, et al. Intracoronary infusion of mononuclear cells from bone marrow or peripheral blood compared with standard therapy in patients after acute myocardial infarction treated by primary percutaneous coronary intervention: results of the randomized controlled HEBE. *Eur Heart J.* 2010;32:1736-1747.